COSMEGEN - dactinomycin injection, powder, lyophilized, for solution
Lundbeck Inc.

Rx only

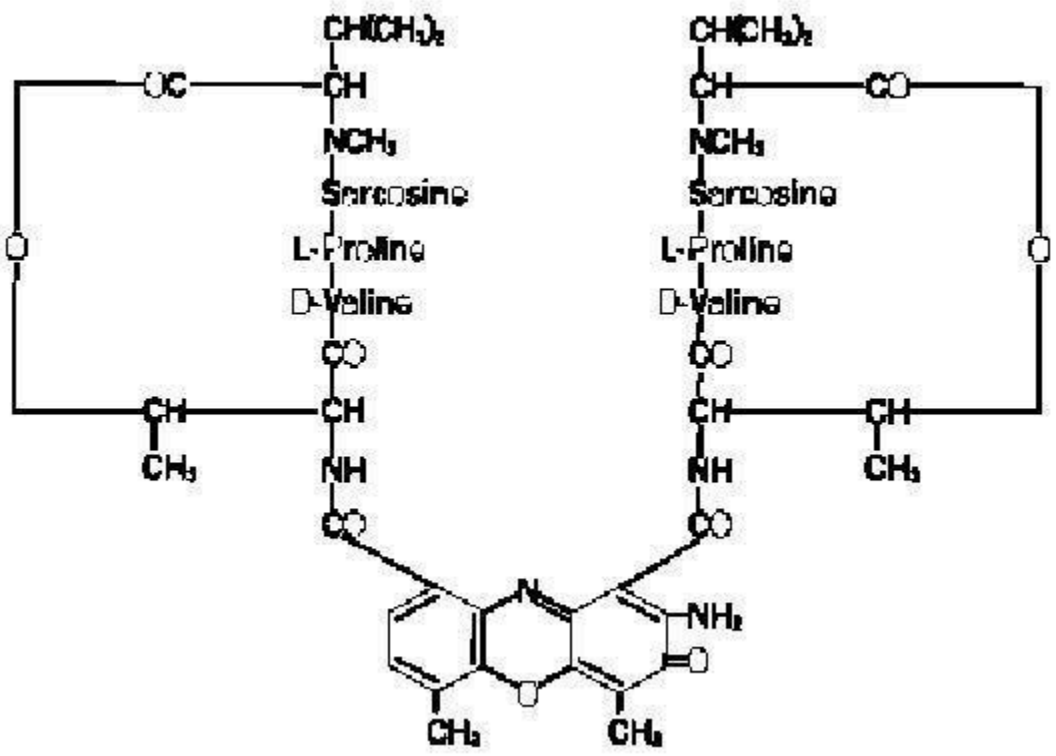
Bar Code

WARNING

COSMEGEN® (Dactinomycin for Injection) should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.
This drug is HIGHLY TOXIC and both powder and solution must be handled and administered with care. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. Due to the toxic properties of dactinomycin (e.g., corrosivity, carcinogenicity, mutagenicity, teratogenicity), special handling procedures should be reviewed prior to handling and followed diligently. Dactinomycin is extremely corrosive to soft tissue. If extravasation occurs during intravenous use, severe damage to soft tissues will occur. In at least one instance, this has led to contracture of the arms.

DESCRIPTION

Dactinomycin is one of the actinomycins, a group of antibiotics produced by various species of *Streptomyces*. Dactinomycin is the principal component of the mixture of actinomycins produced by *Streptomyces parvullus*. Unlike other species of *Streptomyces*, this organism yields an essentially pure substance that contains only traces of similar compounds differing in the amino acid content of the peptide side chains. The empirical formula is $C_{62}H_{86}N_{12}O_{16}$ and the structural formula is:



COSMEGEN is a sterile, yellow to orange lyophilized powder for injection by the intravenous route or by regional perfusion after reconstitution. Each vial contains 0.5 mg (500 mcg) of dactinomycin and 20.0 mg of mannitol.

CLINICAL PHARMACOLOGY

Action

Generally, the actinomycins exert an inhibitory effect on gram-positive and gram-negative bacteria and on some fungi. However, the toxic properties of the actinomycins (including dactinomycin) in relation to antibacterial activity are such as to preclude their use as antibiotics in the treatment of infectious diseases.

Because the actinomycins are cytotoxic, they have an antineoplastic effect which has been demonstrated in experimental animals with various types of tumor implants. This cytotoxic action is the basis for their use in the treatment of certain types of cancer. Dactinomycin is believed to produce its cytotoxic effects by binding DNA and inhibiting RNA synthesis.

Pharmacokinetics and Metabolism

Results of a study in patients with malignant melanoma indicate that dactinomycin (^{3}H actinomycin D) is minimally metabolized, is concentrated in nucleated cells, and does not penetrate the blood-brain barrier. Approximately 30% of the dose was recovered in urine and feces in one week. The terminal plasma half-life for radioactivity was approximately 36 hours.

CLINICAL STUDIES

A wide variety of single agent and combination chemotherapy regimens with COSMEGEN have been studied. Because chemotherapeutic regimens are constantly changing, the decision to employ COSMEGEN should be directly supervised by physicians familiar with current oncologic practices and new advances in therapy.

Wilms' Tumor

The neoplasm responding most frequently to COSMEGEN is Wilms' tumor. Data from the National Wilms' Tumor Studies (NWTS-1, NWTS-2, NWTS-3 and NWTS-4) support the use of COSMEGEN in Wilms' tumor. The NWTS-3 evaluated results in 1,439 patients randomized to various regimens incorporating COSMEGEN (see table below).[1]

The Third National Wilms' Tumor Study

Stage	Regimen	4-Year Relapse Free Survival (%)	4-Year Overall Survival (%)
I (favorable histology)	L	89.0	95.6
	EE	91.8	97.4
II (favorable histology)	DD	87.9	93.6
	DD2	86.9	89.6
	K	87.4	91.1
	K2	90.1	94.9
III (favorable histology)	DD1	82.0	90.9
	DD2	85.9	86.7
	K1	71.4	85.2
	K2	76.8	85.1
IV (favorable histology)	DD-RT	71.9	78.4
	J	77.9	86.6
I-III (unfavorable histology)	DD-RT	67.1	68.3
	J	62.4	68.4
IV (unfavorable histology)	DD-RT	58.3	58.3
	J	52.9	52.3

L = COSMEGEN and vincristine (10 weeks)

EE = COSMEGEN and vincristine (26 weeks)

DD = COSMEGEN, doxorubicin, and vincristine (65 weeks)

DD1 = COSMEGEN, doxorubicin, and vincristine (65 weeks) preceded by radiation therapy (1000 rads)

DD2 = COSMEGEN, doxorubicin, and vincristine (65 weeks) preceded by radiation therapy (2000 rads)

DD-RT = COSMEGEN, doxorubicin, and vincristine (65 weeks) preceded by radiation therapy (dose according to age)

K = COSMEGEN and vincristine (65 weeks)

K1 = COSMEGEN and vincristine (65 weeks) preceded by radiation therapy (1000 rads)

K2 = COSMEGEN and vincristine (65 weeks) preceded by radiation therapy (2000 rads)

J = COSMEGEN, doxorubicin, cyclophosphamide, and vincristine (65 weeks)

It should be noted that the complete results from NWTS-4 have not yet been published. Changes in NWTS-4 and NWTS-5 have consisted of alterations in duration as well as dose intensity of COSMEGEN. As a consequence, appropriate consultation with physicians experienced in the management of Wilms' tumor should be sought.

Childhood Rhabdomyosarcoma

The Third Intergroup Rhabdomyosarcoma Study (IRS-III) studied 1,062 previously untreated pediatric patients and young adults (≤21 years of age) and compared outcomes amongst a number of treatment regimens.

COSMEGEN was included in all arms as a standard component of the treatment regimen; thus, comparative data are not available from this study. Nevertheless, it does provide information on treatment outcomes in a large group of closely studied patients. For treatment purposes, patients were stratified according to clinical group, histologic subtype, and site of disease. Patients in most strata were randomized, but clinical group I patients with favorable histology were not randomized and treated according to a single regimen.[2]

The Third Intergroup Rhabdomyosarcoma Study

Group	Number of Arms	Chemotherapy Regimen	5-Year Progression Free Survival (%) (mean±SEM)	5-Year Overall Survival (%) (mean±SEM)
I (favorable histology)	1 (non-randomized)	cyclic sequential VA (1 year)	83±3	93±2
II (favorable histology, excluding orbit, head and paratesticular sites)	2 (randomized)	VA, doxorubicin and RT (1 year) VA and RT (1 year)	77±6 56±10	89±5 54±13
III (excluding special pelvic, orbit, scalp, parotid, oral cavity, larynx, oropharynx and cheek)	3 (randomized)	pulsed VAC and RT (2 years) pulsed VADRC-VAC, CDDP and RT (2 years) pulsed VADRC-VAC, CDDP, VP-16 and RT (2 years)	70±6 62±5 56±4	70±6 63±5 64±5
IV (all)	3 (randomized)	pulsed VAC and RT (2 years) pulsed VADRC-VAC, CDDP and RT (2 years) pulsed VADRC-VAC, CDDP, VP-16 and RT (2 years)	27±8 27±8 30±6	27±6 31±6 29±7

VA = vincristine/COSMEGEN
VADRC = vincristine/doxorubicin/cyclophosphamide
VAC = vincristine/COSMEGEN/cyclophosphamide
CDDP= Cisplatin
VP-16 = Etoposide
RT = radiation therapy

Metastatic Nonseminomatous Testicular Cancer

Combinations of vinblastine, cyclophosphamide, COSMEGEN, bleomycin and cisplatin (VAB-6 regimen) have been employed in the treatment of metastatic nonseminomatous testicular cancer.[3,4] In a retrospective analysis of 142 evaluable patients with primary advanced stage II or clinical stage III testicular cancer 112 (79%) achieved a complete response (CR) after treatment with VAB-6 alone or in combination with surgery. Relapses were uncommon (12%) and 117 of 166 patients (71%) were categorized as alive without evidence of disease during the four years covered by the study.

Ewing's Sarcoma

COSMEGEN in conjunction with vincristine, doxorubicin, cyclophosphamide and radiotherapy has been used in the management of both metastatic and non-metastatic Ewing's sarcoma. Of 120 previously untreated patients with non-metastatic disease treated with COSMEGEN as part of maintenance therapy in the United Kingdom Children's Cancer Study Group Ewing's Tumor Study (ET-1), 49 (41%) were free of disease at 5 years and 53 (44%) were alive at 5 years.[5] Outcomes in regional and metastatic disease for previously untreated patients administered COSMEGEN resulted in 31 of 44 patients (70%) achieving a CR after a median time on study of 83 weeks. Eight of 44 (18%) patients achieved a partial response (PR) and the remaining 5 (11%) demonstrated no response to the regimen.[6]

Gestational Trophoblastic Neoplasia

Single agent COSMEGEN has been used in the management of nonmetastatic gestational trophoblastic neoplasia. In a series of 31 patients with nonmetastatic disease, complete and sustained remissions were achieved with COSMEGEN alone in 94% of treated patients.[7] Alternating combination regimens incorporating COSMEGEN in conjunction with etoposide, methotrexate, vincristine and cyclophosphamide (EMA-CO regimen)[8] have also been used in the treatment of poor prognosis gestational trophoblastic neoplasia. Administration of EMA-CO to 148 women with poor prognosis gestational trophoblastic neoplasia resulted in 110 (80%) complete and 25 (18%) partial responses after a mean follow-up of 50.4 months. Overall survival during the study period was 85% and relapses were uncommon (5.4%). Meticulous monitoring of beta-hCG (human chorionic gonadotropin) must be incorporated into the treatment regimen.

Regional Perfusion in Locally Recurrent and Locoregional Solid Malignancies

COSMEGEN, as a component of regional perfusion, has been administered as palliative treatment and as an adjunct to tumor resection in the management of locally recurrent and locoregional sarcomas, carcinomas and adenocarcinomas.

INDICATIONS AND USAGE

COSMEGEN, as part of a combination chemotherapy and/or multi-modality treatment regimen, is indicated for the treatment of Wilms' tumor, childhood rhabdomyosarcoma, Ewing's sarcoma and metastatic, nonseminomatous testicular cancer.

COSMEGEN is indicated as a single agent, or as part of a combination chemotherapy regimen, for the treatment of gestational trophoblastic neoplasia.

COSMEGEN, as a component of regional perfusion, is indicated for the palliative and/or adjunctive treatment of locally recurrent or locoregional solid malignancies.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

COSMEGEN should not be given at or about the time of infection with chickenpox or herpes zoster because of the risk of severe generalized disease which may result in death.

WARNINGS

Reports indicate an increased incidence of second primary tumors (including leukemia) following treatment with radiation and antineoplastic agents, such as COSMEGEN. Multi-modal therapy creates the need for careful, long-term observation of cancer survivors.

Pregnancy Category D

COSMEGEN may cause fetal harm when administered to a pregnant woman. COSMEGEN has been shown to cause malformations and embryotoxicity in rat, rabbit, and hamster when given in doses of 50-100 mcg/kg (approximately 0.5-2 times the maximum recommended daily human dose on a body surface area basis). If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential must be warned to avoid becoming pregnant.

PRECAUTIONS

General

This drug is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care (see boxed warning and HOW SUPPLIED, *Special Handling*). Since COSMEGEN is extremely corrosive to soft tissues, it is intended for intravenous use. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling COSMEGEN. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse (see HOW SUPPLIED, *Special Handling*).

As with all antineoplastic agents, COSMEGEN is a toxic drug and very careful and frequent observation of the patient for adverse reactions is necessary. These reactions may involve any tissue of the body, most commonly the hematopoietic system resulting in myelosuppression. As such, live virus vaccines should not be administered during therapy with COSMEGEN. The possibility of an anaphylactoid reaction should be borne in mind.

It is extremely important to observe the patient daily for toxic side effects when combination chemotherapy is employed, since a full course of therapy occasionally is not tolerated. If stomatitis, diarrhea, or severe hematopoietic depression appear during therapy, these drugs should be discontinued until the patient has recovered.

Veno-occlusive Disease

Veno-occlusive disease (primarily hepatic) may result in fatality, particularly in children younger than 48 months. (See ADVERSE REACTIONS, *Hepatic*.)

COSMEGEN (Dactinomycin for Injection) and Radiation Therapy

An increased incidence of gastrointestinal toxicity and marrow suppression has been reported with combined therapy incorporating COSMEGEN and radiation. Moreover, the normal skin, as well as the buccal and pharyngeal mucosa, may show early erythema. A smaller than usual radiation dose administered in combination with COSMEGEN causes erythema and vesiculation, which progress more rapidly through the stages of tanning and desquamation. Healing may occur in four to six weeks rather than two to three months. Erythema from previous radiation therapy may be reactivated by COSMEGEN alone, even when radiotherapy was administered many months earlier, and especially when the interval between the two forms of therapy is brief. This potentiation of radiation effect represents a special problem when the radiotherapy involves the mucous membrane. When irradiation is directed toward the nasopharynx, the combination may produce severe oropharyngeal mucositis. *Severe reactions may ensue if high doses of both COSMEGEN and radiation therapy are used or if the patient is particularly sensitive to such combined therapy.*

Particular caution is necessary when administering COSMEGEN within two months of irradiation for the treatment of right-sided Wilms' tumor, since hepatomegaly and elevated AST levels have been noted. In general, COSMEGEN should not be concomitantly administered with radiotherapy in the treatment of Wilms' tumor unless the benefit outweighs the risk.

COSMEGEN (Dactinomycin for Injection) and Regional Perfusion Therapy
Complications of the perfusion technique are related mainly to the amount of drug that escapes into the systemic circulation and may consist of hematopoietic depression, absorption of toxic products from massive destruction of neoplastic tissue, increased susceptibility to infection, impaired wound healing, and superficial ulceration of the gastric mucosa. Other side effects may include edema of the extremity involved, damage to soft tissues of the perfused area, and (potentially) venous thrombosis.

Laboratory Tests
Many abnormalities of renal, hepatic, and bone marrow function have been reported in patients with neoplastic diseases receiving COSMEGEN. Renal, hepatic, and bone marrow functions should be assessed frequently.

Drug/Laboratory Test Interactions
Dactinomycin may interfere with bioassay procedures for the determination of antibacterial drug levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Reports indicate an increased incidence of second primary tumors (including leukemia) following treatment with radiation and antineoplastic agents, such as COSMEGEN. Multi-modal therapy creates the need for careful, long-term observation of cancer survivors.
The International Agency on Research on Cancer has judged that dactinomycin is a positive carcinogen in animals. Local sarcomas were produced in mice and rats after repeated subcutaneous or intraperitoneal injection. Mesenchymal tumors occurred in male F344 rats given intraperitoneal injections of 50 mcg/kg, 2 to 5 times per week for 18 weeks. The first tumor appeared at 23 weeks.
Dactinomycin has been shown to be mutagenic in a number of test systems *in vitro* and *in vivo* including human fibroblasts and leukocytes, and HeLa cells. DNA damage and cytogenetic effects have been demonstrated in the mouse and the rat.
Adequate fertility studies have not been reported, although, reports suggest an increased incidence of infertility following treatment with other antineoplastic agents.

Pregnancy
Pregnancy Category D
(See WARNINGS.)

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from COSMEGEN, a decision should be made as to discontinuation of nursing and/or drug, taking into account the importance of the drug to the mother.

Pediatric Use
The greater frequency of toxic effects of COSMEGEN in infants suggest that this drug should be administered to infants only over the age of 6 to 12 months.

Geriatric Use
Clinical studies of COSMEGEN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, a published meta-analysis of all studies performed by the Eastern Cooperative Oncology Group (ECOG) over a 13-year period suggests that administration of COSMEGEN to elderly patients may be associated with an increased risk of myelosuppression compared to younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
Toxic effects (excepting nausea and vomiting) usually do not become apparent until two to four days after a course of therapy is stopped, and may not peak until one to two weeks have elapsed. Deaths have been reported. However, adverse reactions are usually reversible on discontinuance of therapy. They include the following:
Miscellaneous: malaise, fatigue, lethargy, fever, myalgia, proctitis, hypocalcemia, growth retardation, infection.
Oral: cheilitis, dysphagia, esophagitis, ulcerative stomatitis, pharyngitis.
Lung: pneumonitis.
Gastrointestinal: anorexia, nausea, vomiting, abdominal pain, diarrhea, gastrointestinal ulceration. Nausea and vomiting, which occur early during the first few hours after administration, may be alleviated by the administration of anti-emetics.

Hepatic: liver toxicity including liver function test abnormalities, ascites, hepatomegaly, hepatitis, hepatic failure with reports of death, hepatic veno-occlusive disease which may be associated with intravascular clotting disorder and multi-organ failure (see PRECAUTIONS, Veno-occlusive Disease).
Hematologic: anemia, even to the point of aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia, pancytopenia, reticulocytopenia, neutropenia, febrile neutropenia. Platelet and white cell counts should be performed *frequently* to detect severe hematopoietic depression. If either count markedly decreases, the drug should be withheld to allow marrow recovery. This often takes up to three weeks.
Dermatologic: alopecia, skin eruptions, acne, flare-up of erythema or increased pigmentation of previously irradiated skin.
Soft tissues: Dactinomycin is extremely corrosive. If extravasation occurs during intravenous use, severe damage to soft tissues will occur. In at least one instance, this has led to contracture of the arms. Epidermolysis, erythema, and edema, at times severe, have been reported with regional limb perfusion.
Laboratory Tests
Many abnormalities of renal, hepatic, and bone marrow function have been reported in patients with neoplastic diseases receiving COSMEGEN. Renal, hepatic, and bone marrow functions should be assessed frequently.

OVERDOSAGE
Dactinomycin was lethal to mice and rats at intravenous doses of 700 and 500 mcg/kg, respectively (approximately 3.8 and 5.4 times the maximum recommended daily human dose on a body surface area basis, respectively). The oral LD_{50} of dactinomycin is 7.8 mg/kg and 7.2 mg/kg in the mouse and rat, respectively.
Manifestations of overdose in patients have included nausea, vomiting, diarrhea, mucositis including stomatitis, gastrointestinal ulceration, skin disorders including exanthema, desquamation and epidermolysis, severe hematopoietic depression, veno-occlusive disease, acute renal failure, and death. No specific information is available on the treatment of overdosage with COSMEGEN. Treatment is symptomatic and supportive. It is advisable to check skin and mucous membrane integrity as well as renal, hepatic, and bone marrow functions frequently.

DOSAGE AND ADMINISTRATION
Not for oral administration
Toxic reactions due to COSMEGEN are frequent and may be severe (see ADVERSE REACTIONS), thus limiting in many instances the amount that may be administered. However, the severity of toxicity varies markedly and is only partly dependent on the dose employed.
Careful calculation of the dosage should be performed prior to administration of each dose.
Intravenous Use
The dosage of COSMEGEN varies depending on the tolerance of the patient, the size and location of the neoplasm, and the use of other forms of therapy. It may be necessary to decrease the usual dosages suggested below when additional chemotherapy or radiation therapy is used concomitantly or has been used previously.
The dosage for COSMEGEN is calculated in micrograms (mcg). The dose intensity per 2-week cycle for adults or children should not exceed 15 mcg/kg/day or 400-600 mcg/m^2/day intravenously for five days. Calculation of the dosage for obese or edematous patients should be performed on the basis of surface area in an effort to more closely relate dosage to lean body mass.
A wide variety of single agent and combination chemotherapy regimens with COSMEGEN may be employed. Because chemotherapeutic regimens are constantly changing, dosing and administration should be performed under the direct supervision of physicians familiar with current oncologic practices and new advances in therapy. The following suggested regimens are based upon a review of current literature concerning therapy with COSMEGEN and are on a per cycle basis.
Wilms' Tumor, Childhood Rhabdomyosarcoma and Ewing's Sarcoma
Regimens of 15 mcg/kg intravenously daily for five days administered in various combinations and schedules with other chemotherapeutic agents have been utilized in the treatment of Wilms' tumor[1], rhabdomyosarcoma[2] and Ewing's sarcoma.[5,6]
Metastatic Nonseminomatous Testicular Cancer
1000 mcg/m^2 intravenously on Day 1 as part of a combination regimen with cyclophosphamide, bleomycin, vinblastine, and cisplatin.[3]
Gestational Trophoblastic Neoplasia
12 mcg/kg intravenously daily for five days as a single agent.[7]
500 mcg intravenously on Days 1 and 2 as part of a combination regimen with etoposide, methotrexate, folinic acid, vincristine, cyclophosphamide and cisplatin.[8]
Regional Perfusion in Locally Recurrent and Locoregional Solid Malignancies
The dosage schedules and the technique itself vary from one investigator to another; the published literature, therefore, should be consulted for details. In general, the following doses are suggested:
50 mcg (0.05 mg) per kilogram of body weight for lower extremity or pelvis.
35 mcg (0.035 mg) per kilogram of body weight for upper extremity.
It may be advisable to use lower doses in obese patients, or when previous chemotherapy or radiation therapy has been employed.

Preparation of Solution for Intravenous Administration

This drug is **HIGHLY TOXIC** and both powder and solution must be handled and administered with care (see boxed warning and HOW SUPPLIED, *Special Handling*). Since COSMEGEN is extremely corrosive to soft tissues, it is intended for intravenous use. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Appropriate protective equipment should be worn when handling COSMEGEN. Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse. (See HOW SUPPLIED, *Special Handling*.)

Reconstitute COSMEGEN by adding 1.1 mL of **Sterile Water for Injection (without preservative)** using aseptic precautions. The resulting solution of COSMEGEN will contain approximately 500 mcg (0.5 mg) per mL.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. When reconstituted, COSMEGEN is a clear, gold-colored solution.

Once reconstituted, the solution of COSMEGEN can be added to infusion solutions of Dextrose Injection 5 percent or Sodium Chloride Injection either directly or to the tubing of a running intravenous infusion.

Although reconstituted COSMEGEN is chemically stable, the product does not contain a preservative and accidental microbial contamination might result. Any unused portion should be discarded. Use of water containing preservatives (benzyl alcohol or parabens) to reconstitute COSMEGEN for Injection, results in the formation of a precipitate.

Partial removal of COSMEGEN from intravenous solutions by cellulose ester membrane filters used in some intravenous in-line filters has been reported.

Since dactinomycin is extremely corrosive to soft tissue, precautions for materials of this nature should be observed.

If the drug is given directly into the vein without the use of an infusion, the “two-needle technique” should be used. Reconstitute and withdraw the calculated dose from the vial with one sterile needle. Use another sterile needle for direct injection into the vein. Discard any unused portion of the COSMEGEN solution.

Management of Extravasation

Care in the administration of COSMEGEN will reduce the chance of perivenous infiltration (see boxed warning and ADVERSE REACTIONS). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of COSMEGEN, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 minutes q.i.d. for 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.[9]

HOW SUPPLIED

COSMEGEN for Injection is a lyophilized powder. In the dry form the compound is an amorphous yellow to orange powder. The solution is clear, gold-colored and essentially free from visible particles. COSMEGEN for Injection is supplied in vials containing 0.5 mg (500 micrograms) of dactinomycin and 20.0 mg of mannitol.

NDC 67386-811-55

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light and humidity.

Special Handling

Animal studies have shown dactinomycin to be corrosive to skin, irritating to the eyes and mucous membranes of the respiratory tract and highly toxic by the oral route. It has also been shown to be carcinogenic, mutagenic, embryotoxic and teratogenic. Due to the drug's toxic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of COSMEGEN for parenteral administration. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Avoid exposure during pregnancy. The National Institutes of Health presently recommends that the preparation of injectable antineoplastic drugs should be performed in a Class II laminar flow biological safety cabinet.[10] Personnel preparing drugs of this class should wear chemical resistant, impervious gloves, safety goggles, outer garments and shoe covers. Additional body garments should be used based upon the task being performed (e.g., sleevelets, apron, gauntlets, disposable suits) to avoid exposed skin surfaces and inhalation of vapors and dust. Appropriate techniques should be used to remove potentially contaminated clothing.

Several other guidelines for proper handling and disposal of antineoplastic drugs have been published and should be considered.[11-16]

Accidental Contact Measures

Should accidental eye contact occur, copious irrigation for at least 15 minutes with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin

contact occur, the affected part must be irrigated immediately with copious amounts of water for at least 15 minutes while removing contaminated clothing and shoes. Medical attention should be sought immediately. Contaminated clothing should be destroyed and shoes cleaned thoroughly before reuse (see PRECAUTIONS, *General* and DOSAGE AND ADMINISTRATION, *Preparation of Solution for Intravenous Administration*).

REFERENCES

1. D'Angio, G.J.; et al: Treatment of Wilms' Tumor: Results of the Third National Wilms' Tumor Study, Cancer *64:* 349-360, 1989.

2. Crist, W.; et al: The Third Intergroup Rhabdomyosarcoma Study, J. Clin. Oncol. *13:* 610-630, 1995.

3. Vugrin, D.; et al: VAB-6 Combination Chemotherapy in Disseminated Cancer of the Testis, Ann. Intern. Med. *95:* 59-61, 1981.

4. Bosl, G.J.; et al: VAB-6: An Effective Chemotherapy Regimen for Patients With Germ-Cell Tumors, J. Clin. Oncol. *4:* 1493-1499, 1986.

5. Craft, A.W.; et al: Long-Term Results from the First UKCCSG Ewing's Tumour Study (ET-1), Eur. J. Cancer, *33:* 1061-1069, 1997.

6. Vietti, T.J.; et al: Multimodal Therapy in Metastatic Ewing's Sarcoma: An Intergroup Study, Nat. Cancer Inst. Monogr. *56:* 279-284, 1981.

7. Osathanondh, R.; et al: Actinomycin D as the Primary Agent for Gestational Trophoblastic Disease, Cancer, *36:* 863-866, 1975.

8. Newlands, E.S.; et al: Results with the EMA/CO (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine) Regimen in High Risk Gestational Trophoblastic Tumours, 1979 to 1989, Br. J. Obstet. Gynaecol. *98:* 550-557, 1991.

9. Rudolph, R.; Larson, D.L.: Etiology and Treatment of Chemotherapeutic Agent Extravasation Injuries: A Review, J. Clin. Oncol. *5:* 1116-1126, 1987.

10. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

11. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics, JAMA, *253:* 1590-1592, 1985.

12. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

13. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents, Med. J. Australia *1:* 426-428, 1983.

14. Jones, R. B.; et al: Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center, Ca- A Cancer Journal for Clinicians, Sept/Oct, 258-263, 1983.

15. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs, Am. J. Hosp. Pharm. *47:* 1033-1049, 1990.

16. Controlling Occupational Exposure to Hazardous Drugs (OSHA Work-Practice Guidelines), Am. J. Health-Syst. Pharm. *53:* 1669-1685, 1996.

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